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Special Considerations for Paxlovid Treatment Among Transplant Recipients With SARS-CoV-2 Infection

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Novel Agents for the Treatment of COVID-19

The SARS-CoV-2 pandemic has been historic in terms of the number of lives tragically affected and the huge toll of morbidity and mortality (1). During the pandemic's first year there were many drugs employed and formally studied, with at best modest clinical benefits (2). In mid-2021, results of studies with two news drugs brought substantial new hope. Merck and Ridgeback Biotherapeutic's drug, molnupiravir, was reported to reduce death and hospitalization from coronavirus disease 2019 (COVID-19) by 30% (3). Soon after this, Pfizer reported impressive results for its drug, Paxlovid. In this report we will discuss the latter drug and why, despite its great efficacy, it may pose a major safety risk to transplant patients and others treated with calcineurin or mTOR (mammalian target of rapamycin) inhibitors.

Paxlovid, is a combination of two oral drugs. The first, nirmatrelvir (PF-07321332), is a newly developed agent that blocks the SARS-CoV-2-3CL protease, which is important for viral replication. The second drug is ritonavir, which is used only to slow nirmatrelvir metabolism (4). The Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (EPIC-HR) Study is evaluating the efficacy and safety of Paxlovid administered twice daily for five days as treatment of adults with acute COVID-19 (5). It is a placebo controlled, double blind study of patients who are at increased risk of developing severe COVID-19 illness. On November 5, 2021, Pfizer announced results of a scheduled interim analysis of the study (4). The results were dramatic, with an 89% reduction in risk of hospitalization or all-cause mortality compared to placebo. Among patients treated within the first three days of symptoms, by day 28 of follow-up, there were 3/389 hospitalized with no deaths in the Paxlovid group compared to 27/385 hospitalized with 7 deaths in the placebo group ($p<0.0001$). These positive results led the study's data monitoring committee, in consultation with FDA, to recommend cessation of further study

enrollment (at the time of this writing the study continues with existing subjects) (4). On November 16, 2021, the company applied to the FDA seeking emergency use authorization. On December 14, 2021, Pfizer provided additional information, indicating that "in vitro data confirm that nirmatrelvir is a potent inhibitor of the Omicron 3CL protease… indicat[ing] nirmatrelvir's potential to maintain robust antiviral activity against Omicron" (6). On December 22, 2021, Paxlovid received emergency use authorization (EUA) by the FDA (7). Importantly, the EUA includes a contraindication statement for patients on drugs that are "highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions" (8). The list of contraindicated drugs, however, does not include cyclosporine, tacrolimus, or sirolimus, or indeed any mention of calcineurin inhibitors (CNI) or mTOR inhibitors (mTORi) (8). Consequently, it is likely that Paxlovid will be prescribed to many transplant patients.

Potential Interactions with Immunosuppressive Agents

While Paxlovid brings great promise to the fight against COVID-19, for transplant patients it causes significant risk related to drug interactions. Generally, patients with transplants are at high risk of COVID-19 morbidity and mortality due to immunosuppression, lack of response to vaccination, and co-morbid conditions (9,10). With the current surge of COVID-19 and the omicron variant, patients will approach providers seeking Paxlovid prescriptions – which may occur even preemptively, prior to diagnosis of COVID-19. Pfizer stated in a press release, "[Paxlovid] can be prescribed at the first sign of infection or, pending clinical success of the rest of the EPIC development program and subject to regulatory authorization, at first awareness of an exposure" (7). Although patients could benefit greatly from Paxlovid, they may be at significant risk for drug interactions and harm, due to the ritonavir component of Paxlovid, a

particularly potent inhibitor of cytochrome P450 system CYP3A enzymes (11). The interaction between ritonavir and CYP3A dependent drugs can result in increases in area under the curve blood concentrations of these latter drugs between 1.8 and 20-fold (11). Since both cyclosporine, tacrolimus, and mTORi's (sirolimus and everolimus) are highly dependent on CYP3A metabolism, their plasma levels on exposure to ritonavir will increase significantly and rapidly. This effect has been seen previously in reports involving HIV positive transplant patients on ritonavir as a single agent, or as part of a combination drug. One report found an increase in tacrolimus trough from 8.7 ng/ml to 106 ng/ml after only 3 days of starting darunavir/ritonavir, despite a 12% reduction in dose (12). A tacrolimus trough of this level, even if transient, can lead to dangerous side effects including kidney injury, seizures, PRES (posterior reversible encephalopathy) and even death. In other studies, a reduction of CNI dosage of up to 99% -- with tacrolimus doses as low as 0.5 mg once every 7 days – were enough to maintain therapeutic trough levels (13-16). The same effect has been noted with sirolimus (17.) It is important to note that in the pivotal EPIC-HR Study of Paxlovid, a highly relevant exclusion criterion was, "current or expected use of any medications or substances that are highly dependent on CYP3A4 for clearance or are strong inducers of CYP3A4" (5).

In addition to the ritonavir-CNI/mTORi interaction, inhibition of CYP3A can result in dangerous interactions with other drugs that transplant patients are frequently treated with, including HMG CoA reductase inhibitors (statins) as well as calcium channel blockers and anticoagulants such as warfarin. A more detailed list of potential interactions can be referenced in the FDA EUA document (8). The effects of Paxlovid on each of these drugs must be considered.

With Paxlovid treatment for COVID-19, the ritonavir dose is relatively low at 100 mg twice daily and treatment is only for five days. Despite this limited exposure, risk for transplant patients could still be substantial. The risk is amplified by the availability of Paxlovid coinciding with the omicron-driven spike in the number of COVID-19 cases. Risk may also be increased because the combined drug is marketed under a single name, Paxlovid, which may result in providers failing to recognize the ritonavir component. Moreover, transplant patients may turn first not to their nephrologists, but to primary care providers who may not be aware of the ritonavir-CNI/mTORi drug interactions.

Recommendations for Paxlovid Treatment and Risk Mitigation in Transplant Recipients

Although current experience in dose adjustment does not exist, based on existing data with ritonavir we suggest an empirical reduction or withholding of CNI administration after initiation of Paxlovid and basing subsequent CNI dosing on trough drug levels for at least as long as Paxlovid treatment continues. Once Paxlovid treatment concludes, the original dose of CNI may be resumed but monitoring trough levels for one or two days seems prudent given the circulating half-life of ritonavir is 3-5 hours and its CYP3A effect could last somewhat longer. The timing of when and how to restart the CNI/mTORi should weigh the urgency of restarting against the possibility of residual CYP3A4 inhibition. It is important to note that these recommendations are only suggestions, and dosing strategies should be individualized based on the ability to obtain immunosuppressive level monitoring as well as baseline CNI dose and CYP3A polymorphisms, if known. Finally, above and beyond drug interactions, Paxlovid also requires renal dose adjustment, with dose reduction suggested for an eGFR between 30 to 60 ml/min/1.73m2, and the drug is not recommended in patients with an eGFR < 30ml/min/1.73m2 (8).

Given the high risk of drug-drug interaction, hospital and health systems should undertake monitoring and decision support for the use of Paxlovid (Box). Like many other forms of patient safety monitoring and drug safety, a multimodal approach is most likely to be effective. We recommend widespread educational outreach through grand rounds and other lectures; email notifications and information embedded within other COVID-19 updates; partnership outreach to local pharmacies alerting them to Paxlovid-CNI/mTORi interactions; interruptive alerts or other point of prescribing notifications embedded within the electronic health record; automated inbox or tasking to prescribing providers; and automated reports to identify all health system or practice patients on chronic CNI/mTORi newly prescribed Paxlovid, which would allow proactive patient contact and CNI/mTORi dose adjustments. Additionally, other therapies for COVID-19 prevention or treatment exist, which may be an alternative to Paxlovid and may mitigate the risks of drug interactions for patients already taking CNI or MTORi's. Tixagevimab/cilgavimab (Evusheld) is a monoclonal antibody for pre-exposure prophylaxis for immunocompromised patients, and sotrovimab is a monoclonal antibody for treatment of COVID-19 with efficacy against the omicron variant.

In conclusion, Paxlovid is a highly promising new drug combination for treatment of COVID-19. In this review we have discussed important safety risks for patients with transplants or kidney disease that this drug conveys. Yet, these patients are at higher risk related to COVID-19, and there is a great need for an efficacious new agent like Paxlovid. Clinicians must individualize treatment, determining whether Paxlovid's substantial efficacy outweighs risks in the context of individual patients. When treatment is initiated caution and vigilance should be maintained and the risk management strategies described above employed as appropriate.

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Box 1. Paxlovid in Transplant Patients: Dosing Issues and Risk Mitigation Strategies

Dosing Recommendations

- Reduce or hold calcineurin inhibitor dose following first dose of Paxlovid
- Base subsequent dosing on trough levels
- If trough below target goal, administer single dose of calcineurin inhibitor
- Resume normal calcineurin inhibitor dose once treatment course of Paxlovid concludes

Note that these are only recommendations and should be individualized based on the ability to obtain immunosuppressive level monitoring, as well as baseline calcineurin inhibitor dose and CYP3A polymorphisms, if known. Similar strategies can be employed for other drugs, including MTOR inhibitors.

Risk Mitigation Strategies

Health Systems:

- Educational outreach through all applicable channels
- Email notifications and information embedded within other COVID-19 updates
- Partnership outreach to pharmacies alerting them to Paxlovid-calcineurin inhibitor interactions
- Interruptive alerts or other point of prescribing notifications embedded within the electronic health record
- Tasking or inbox alerts to prescribing providers
- Automated reports to identify all health system or practice patients on chronic calcineurin inhibitor therapy newly prescribed Paxlovid
- Because of the multiple medications that could be affected by Paxlovid treatment, inclusion of pharmacists in medication management

Nephrologists, Transplant Programs and Related Providers:

- Identify patients in practice currently treated with calcineurin inhibitors
- Email or other notification to patients
- Discuss potential Paxlovid issues during office visits
- Outreach to referring primary care physicians to inform on Paxlovid drug interactions